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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 12/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,099	VAILLANT ET AL.	
	Examiner	Art Unit	
	Louise Wang, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *3-13,21-25 and 33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,14-20 and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Office acknowledges the receipt of Applicant's election, filed on 24 October 2005. Applicant elects Group I, claims 1, 2, and 14-32, with traverse.

The traversal is on the grounds that there is unity of invention between the claims and that there is no burden in examining the different Inventions together. Applicant's traversal is unpersuasive for the following reasons:

(1) Applicant's contention that the unity of invention standard be adhered to is not appropriate in this case because this U.S. application is a continuation of a PCT and is therefore, not available for filing under U.S.C. §371.

(2) While a search of the prior art for one group may overlap with that of another group, the searches are not co-extensive and thus would be an undue burden on Office resources even if the Groups were placed in the same class and subclass. The PTO classification is merely an administrative convenience and is not dispositive of relatedness of applications.

(3) Applicants' contention that "the Examiner opens the door to re-grouping Groups I and II when stating that the method and claims would both belong to the same invention if Applicants can show that the composition cannot be used other than with the method and vice-versa" is inappropriate. As indicated in the prior Office Action, Examiner's position was that Inventions related as product and process of use can be shown to be distinct. Apparently, Applicants did not appreciate the Examiner's statement that the method can be practiced with another materially different product

such as protease inhibitors, reverse transcriptase inhibitors, and integrase inhibitors, or combinations thereof, which clearly indicates that the inventions are distinct as per MPEP §806.05(h).

(4) There seems to be a lack of support for the Applicant's assertion that "currently, no treatments of HIV infections are available". At the time this application was filed, the products stated above were well known and commercially available for treating HIV infection.

(5) Applicants' citations of MPEP § 806.04 and § 806.05 and the reminder about the two criteria for proper requirement for restriction, establishment of distinctiveness and search burden, further support the Examiner's position. See prior Office Action for the rationales used to establish distinctiveness and search burden.

(6) Applicants' contention of the common utility to the sequences claimed in the application is improper because each nucleotide sequence is not considered to be a proper member of a Markush group. See M.P.E.P. § 803.02. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

The instant claims are drawn to multiple oligonucleotides, which are considered to be unrelated, since each sequence claimed is structurally and functionally independent and distinct due to their unique nucleotide sequence and there is no alignment between the sequences to show significant similarity. As such, the

sequences in the instant claims are not considered to constitute a proper Markush group/genus, and are therefore subject to restriction. Furthermore, a search of more than one of the sequences present in these claims presents an undue burden on the Patent and Trademark Office due to the complex nature of the search in terms of computer time needed to perform the search and the subsequent analysis of the search results by the Examiner. In view of the foregoing, one sequence is considered to be a reasonable number of sequences for examination. Accordingly, Applicants are required to elect one sequence.

(7) It is noted that the Applicants elected claims directed to a method and thereby lost the right to rejoinder of the product and process claims under *In re Ochiai*. See the prior Office Action.

The restriction among the different products that may be used in the claimed methods is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-38 are pending. Claims 3-13, 21-25 and 33-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction election requirement in the reply filed on 24 October 2005.

Claims 1, 2, 14-20, and 26-32 are examined in the instant application and read to the elected sequences, REP 2015, a random 40-mer of wobble nucleotide with no modification, and REP 2031, a poly-C 40-mer with phosphorothioate linkage at every position.

Specification

The disclosure is objected to because of the following informalities:

The specification refers to ON, PS-ODN and PO-ODN on pages 7, 8 and 10, respectively, without first identifying these terms by their complete names.

The word "phosphorothioate" is misspelled in the first line of paragraph 34 on page 8. The words "selected abbreviations", "spectrum", "requirement" and "sequence" in section titles on pages 33, 36, 37, and 50, respectively, are each missing an "e". The word "oligonucleotides" in the section title on page 52 are missing two "o's".

Appropriate correction is required.

The specification is objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID NOs. to all mentions of specific sequences in the specification. See 37 CFR § 1.821(d). Applicants' attention is drawn specifically to Table I, which is a list of sequences without SEQ ID NOs. A reply that fails to comply will be considered to be non-responsive and may result in ABANDONMENT of this application.

Information Disclosure Statement

The specification is replete with citations of references. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Double patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 14-20, and 26-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3,

5, 7-10, 12-14, 18-20, 28, and 29 of copending Application No. 11/661,403. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed method for the prophylaxis or treatment of a HIV infection is encompassed by, and thus, anticipates the genus method for the prophylaxis or treatment of a viral infection in the copending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the limitation "said anti-HIV activity" in the second last sentence. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 14-20 and 26-32 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for *in vitro* inhibition of part of the HIV life cycle in cell culture, does not reasonably provide enablement for the prophylaxis or treatment of a HIV infection *in vivo*, especially if the subject is a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice/make and use the invention commensurate in scope with these claims.

Claims 1, 2, 14-20 and 26-32 are directed to a method for the prophylaxis or treatment of a HIV infection in a subject comprising administering at least one oligonucleotide that is at least 29 nucleotides in length and that binds in a non-sequence complementary mode.

The guidance presented in the specification is limited to three *in vitro* cell culture assays: (1) MTT assay for cytopathic effect; (2) inhibition of the replication of HIV *env* gene (Example 4) by oligonucleotides, REP 2003, 2004, 2006, and 2007, which are different from the elected oligonucleotides, REP 2015 and 2031; and (3) drug susceptibility assay for expression of p24 *gag* (Example 10), which all have the art-recognized limitation of high level of assay variability between virus cultures. All *in vitro* tests are unreliable in detecting the drug susceptibility of minority HIV-1 variants in the virus population. Resistant mutants may not persist at detectable levels in the absence of drug selection pressure, which increases the complexity in extrapolating from *in vitro* to *in vivo* test results.

An *in vitro* result of reduced cell viability or less HIV *env* gene replication is nowhere near an indication of the effectiveness of this oligonucleotide "for the prophylaxis or treatment of a HIV infection in a subject," as recited in the instant claims, but a working hypothesis or speculation, because an *in vitro* system is over-simplified compared to the body of an HIV-infected subject and is not predictive of, nor correlate with, the complex interactions of natural HIV infections in subjects such as humans. Due to the highly unpredictable nature of HIV-infection, extrapolating from *in vitro* models to whole organisms without *in vivo* validation is hazardous and unpredictable.

Given the divergence of *in vitro* and *in vivo* HIV-specific immune responses, the clinical relevance of the disclosed measurements in the instant application is uncertain. One skilled in the art would be burdened with an undue quantity of *in vivo* experiments in order to make and use the current invention since the applicants have not provided any clear-cut evidence to demonstrate that the claimed oligonucleotides, REP 2015 and REP 2031, can prevent or treat HIV infection when the subjects encompass *in vivo* application. Absent working examples and specific teachings of the clinical efficacy, therapeutic index, and pharmacokinetic properties of the oligonucleotides, those in the art would not be able to use the claimed method for the prophylaxis or treatment of HIV infection with REP 2015 and REP 2031.

Considering the lack of data or working examples in the specification, the broad scope of the claims, the complex state and nature of the art, and the teachings regarding unpredictability in this art, the Applicant has not provided sufficient information

to enable those skilled in the art to practice the claimed method *in vivo* without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 14-17, 28, and 30-32 are rejected under 35 U.S.C. §102(b) as being anticipated by Andreola *et al.* (2001).

Claims 1, 14-17, 28, and 30-32 read on an *in vitro* method for the treatment of a HIV infection in a cell culture comprising administering the following:

(a) A mixture of at least two different antiviral oligonucleotides;

(b) The oligonucleotides are non-complementary to HIV sequence;

(c) The oligonucleotides bind to viral components;

(d) At least one oligonucleotide comprises at least one antiviral randomer;

(e) The formulation of oligonucleotides has an IC_{50} of 0.05 μM or less for HIV.

(f) The oligonucleotides are at least 29 nucleotides long; and

(g) The oligonucleotides are at least 40 nucleotides long.

Andreola *et al.* teaches a plurality of non-complementary anti-HIV random oligonucleotides (page 10089, figure 1) that bind to the HIV component, RNase H. Two of the oligonucleotides are 81 nucleotides long and have an IC_{50} of 30 nM for HIV

infectivity in cell culture (page 10092, right column and figure 7), which meets the *in vitro* limitation of the claimed method.

Thus, Claims 1, 14-17, and 28-32 are anticipated by Andreola *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 14-16, 18-20, 26, and 28-31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Marshall *et al.* (1992) in view of Mergny *et al.* (1998) and Matsukura *et al.* (1987).

Claims 1, 14-16, 18-20, 26, and 28-31 read on an *in vitro* method for the treatment of a HIV infection in cell cultures comprising administering the following:

(a) A mixture of at least two different antiviral oligonucleotides;

(b) The oligonucleotides are non-complementary to HIV sequence;

(c) The oligonucleotides bind to viral components;

(d) At least one oligonucleotide comprises at least one randomer;

(e) The formulation of oligonucleotides has an IC_{50} of 0.05 μM or less for HIV.

(f) The oligonucleotides are at least 29 nucleotides long;

(g) Each oligonucleotide comprises at least one phosphorothioate linkage;

(h) The oligonucleotide is linked to a molecule to obtain consisting of higher stability, lower serum interaction, higher cellular uptake, higher viral protein interaction, an improved ability to be formulated for delivery, a detectable signal, higher antiviral activity, better pharmacokinetic properties, specific tissue distribution, or lower toxicity; and

(i) The sequence of the oligonucleotide is derived from a viral genome.

Marshall *et al.* teaches the method of inhibition of HIV activity by phosphorothioate oligodeoxycytidines, with an IC_{50} of 0.01 μM (page 6267, Table 1). These oligonucleotides bind to HIV reverse transcriptase and gp120 in a non-sequence-complementary manner. Linkage of these oligonucleotides to phosphorothioate obtains resistance to nuclease (page 6265, see Introduction), a nucleotide degenerative enzyme, and, in turn, achieves higher stability, higher viral interaction and higher antiviral activity.

Marshall *et al.* does not teach the anti-HIV oligonucleotide as long as 29 nucleotides but emphasizes that phosphorothioate oligomers of greater length are required for potent inhibition, as evidenced by the IC_{50} values of various lengths.

Mergny *et al.* teaches phosphorothioate-linked cytosine-rich 29-mers, which form a tetrad of two duplexes "zipped together" in an anti-parallel fashion (page 4797, see Introduction) and have extremely high stability as compared to shorter oligomers (page 4800, Table 1). Mergy *et al.* provides the motivation for modification of the length of the

oligonucleotides by suggesting that these oligonucleotides might have an effect on the uptake, stability, cellular localization and effect of the molecule.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to increase the length of the phosphorothioate oligonucleotides to 29 nucleotides for the purpose of increasing the potency of anti-HIV oligonucleotides. One skilled in the art would have been motivated to make that modification with a reasonable expectation of success *in vitro* because the cytosine-rich phosphorothioate 29-mers have higher stability, cellular uptake and localization.

Marshall *et al.* does not teach any random oligonucleotide derived from a viral genome. However, Matsukura *et al.* teaches randomers derived from *art/trs* region in the HIV genome (page 7707, Figure 1) and suggests combining a phosphorothioate oligodeoxycytidines with a different HIV inhibitor to enhance antiviral activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine at least two anti-HIV oligonucleotides into a composition. One of ordinary skill in the art would have been motivated to make that combination because the mixture of oligonucleotides can simultaneously target different sites of HIV, and would have a reasonable expectation of success in cell cultures because the HIV strains that become resistant to the oligonucleotide randomer may be susceptible to the phosphorothioate oligonucleotide in the mixture, and vice versa.

Thus, claims 1, 14-16, 18-20, 26, and 28-31 are obvious over Marshall *et al.* (1992) in view of Mergny *et al.* (1998) and Matsukura *et al.* (1987).

Remarks

No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Wang whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Louise Wang, Ph.D.
Patent Examiner
30 November 2005

JEFFREY STUCKER
PRIMARY EXAMINER